Annals of Clinical and Analytical Medicine
Original Research

Evaluating the diagnostic efficacy of secretoneurin in ıdentifying heart failure among dyspneic patients in the emergency department

Tahir Talat Yurttaş[1], Ali Cankut Tatliparmak[2], Sarper Yilmaz[3], Asım Bedri Erdem[4], Özgür Dikme[4], Özlem Dikme[4]
[1] Department of Emergency Medicine, Faculty of Medicine, Istanbul Yeni Yuzyil University
[2] Department of Emergency Medicine, Faculty of Medicine, Uskudar University
[3] Department of Emergency Medicine, Faculty of Medicine, Istanbul Dr. Lutfi Kirdar City Hospital
[4] Department of Emergency Medicine, Faculty of Medicine, Istanbul Training and Research Hospital, Istanbul, Turkey

Abstract
Aim: The accurate and timely diagnosis of heart failure is crucial for optimal patient management. This study aimed to evaluate the diagnostic potential of secretoneurin, a novel biomarker, in patients presenting with dyspnea to the emergency department.
Material and Methods: The study included 51 patients, 19 of whom were diagnosed with heart failure, and 32 patients without heart failure. Secretoneurin levels were measured and compared with established biomarkers, N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity cardiac troponin-t (hs-cTnT), for diagnostic utility.
Results: The study findings revealed a significant elevation of secretoneurin levels in heart failure patients compared to those without heart failure ($p<0.001$). In addition, secretoneurin exhibited moderate discriminative properties (AUROC: 0.643, 95% CI: 0.457 - 0.828) when differentiating heart failure from non-heart failure patients. However, NT-proBNP (AUROC: 0.864, 95% CI: 0.739 - 0.99) and hs-cTnT (AUROC: 0.759, 95% CI: 0.596 - 0.922) demonstrated superior diagnostic performance.
Discussion: Secretoneurin is promising as a potential diagnostic biomarker for heart failure, with elevated levels observed in heart failure patients. Further investigations are warranted to determine its precise role and potential contribution as part of a comprehensive diagnostic approach.

Keywords
Secretoneurin, Heart Failure, Dyspnea, Diagnostic Biomarker, Emergency Department.

DOI: 10.4328/ACAM.21783 Received: 2023-06-07 Accepted: 2023-07-10 Published Online: 2023-07-15 Printed: 2023-11-01 Ann Clin Anal Med 2023;14(11):1025-1028
Corresponding Author: Ali Cankut Tatliparmak, Department of Emergency Medicine, Faculty of Medicine, Uskudar University, Istanbul, Turkey.
E-mail: alicankut@gmail.com P: +90 216 400 22 22
Corresponding Author ORCID ID: https://orcid.org/0000-0002-6729-5021
This study was approved by the Ethics Committee of Health Sciences University Istanbul Training and Research Hospital Ethics Committee (Date: 2021-06-04, No: 2864)

Introduction

In emergency medicine, expeditious and accurate diagnosis is pivotal, significantly influencing patient outcomes [1]. One such diagnostic challenge often encountered is the differentiation of dyspnea etiology in patients [2]. Amidst the plethora of possibilities, heart failure tends to be a recurrent determinant of this presentation [3]. Traditional cardiovascular biomarkers, including B-type natriuretic peptides (BNPs) signifying cardiomyocyte stress, and cardiac-specific troponins, indicating cardiomyocyte injury, have indeed found their place in contemporary clinical practice [4–6]. Yet, they fall short of providing a comprehensive understanding of the ongoing pathophysiology, particularly concerning aspects such as neuroendocrine tone and cardiomyocyte Ca+2 homeostasis. Such limitations subtly underscore the persistent need for additional, perhaps more nuanced, biomarkers in heart failure.

Secretoneurin, a derivative of secretogranin II, belonging to the chromogranin-secretogranin (granin) family of proteins implicated in cardiac pathophysiology, enters the arena of promising biomarkers [7]. Secretoneurin's emergence arises from the proteolytic activity of PC1/3 and PC2 on secretogranin II, with their activity seen to triple in failing myocardium [8]. Circulating secretoneurin levels have been reported to elevate in heart failure patients, rendering it a potential marker of interest [9]. Furthermore, animal models have demonstrated secretoneurin's beneficial influence on myocardial ischemia/reperfusion injury, reduction of cardiomyocyte apoptosis, promotion of angiogenesis, and improvement of left ventricular function post-myocardial infarction [10,11]. This intriguing array of attributes lends credence to the hypothesis that secretoneurin might not only be a mere bystander marker but also an active player influencing the disease process.

In light of the aforementioned considerations, this study primarily aims to elucidate secretoneurin's diagnostic utility as a biomarker in patients presenting with undifferentiated dyspnea to the emergency department. More specifically, the study will investigate whether secretoneurin levels differ significantly between patients ultimately diagnosed with heart failure and those with alternative etiologies of dyspnea. Through this inquiry, it is hoped that the diagnostic landscape of heart failure will be further enriched, ultimately guiding more accurate and timely interventions.

Material and Methods

Study Design

This study utilized a cross-sectional design to evaluate the diagnostic accuracy of secretoneurin for heart failure diagnosis in patients presenting to the emergency department with symptoms of shortness of breath.

Selection of Participants

A total of 51 consecutive patients over the age of 18 who presented to the emergency department of Istanbul Training and Research Hospital between September 2021 and October 2021 with chief complaint of shortness of breath and Canadian Triage and Acuity Scale of 1 or 2 were enrolled in the study [12]. Patients with a known diagnosis of heart failure with reduced ejection fraction, patients undergoing cardiopulmonary resuscitation within the emergency department and patients with altered mental status were excluded from the study.

Data Collection

Clinical and laboratory data were collected from each participant upon enrollment. The variables of interest included age, sex, secretoneurin levels, procalcitonin levels, high sensitivity cardiac troponin-t (hs-cTnT) levels, C-reactive protein (CRP) levels, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Age was recorded as a continuous variable, while sex was categorized as male or female. Secretoneurin, procalcitonin, hs-cTnT, CRP, and NT-proBNP levels were measured using standard laboratory methods.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were presented as mean ± standard deviation or median with interquartile range, depending on the distribution. Categorical variables were presented as frequencies and percentages. The independent t-test or Mann-Whitney U test was used to compare continuous variables between patients with and without heart failure, based on the normality assumption. The chi-square test or Fisher's exact test was used to compare categorical variables. A p-value less than 0.05 was considered statistically significant.

Ethical Considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of Health Sciences University Istanbul Training and Research Hospital Ethics Committee (4/6/2021 no: 2864). Informed consent was obtained from each participant prior to enrollment in the study.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Fifty-one patients were enrolled in the study and categorized into two groups based on their definitive diagnoses: heart failure (n=19) and no heart failure (n=32) (Table 1). The mean age of the study participants was 67.70 ± 12.28 years, with no statistically significant difference observed between the groups (heart failure: 70.28 ± 13.19; no heart failure: 66.10 ± 11.63; p=0.262). Of the total number of patients, 25 were female (49%), and there was no statistically significant difference in gender distribution between the two groups (p=0.691).

Regarding biomarker analysis, there was no statistically significant difference in procalcitonin levels between the heart failure group (median: 0.073, IQR: 0.05 - 0.146) and the group without heart failure (median: 0.065, IQR: 0.05 - 0.151) (p=0.676). However, the median hs-cTnT level was significantly lower in the group without heart failure (median: 0.011, IQR: 0.005 - 0.015) compared to the heart failure group (median: 0.02, IQR: 0.016 - 0.039) (p<0.001). Similarly, there was no statistically significant difference in CRP levels between the two groups (no-heart failure group median: 16.2, IQR: 6.9 - 52; heart failure group median: 18.45, IQR: 5.28 - 47.25; p=0.955). However, the median NT-proBNP level was significantly lower in the group without heart failure (median: 200.5, IQR: 85 - 661.28) compared to the heart failure group (median: 4044, IQR: 1787 - 9384) (p<0.001). Moreover, the average secretoneurin

Table 1. Comparison of groups with and without heart failure

	Total (n=51)	No heart failure (n=32)	Heart failure (n=19)	p value	Mean difference (95% CI)
Age (in years)	67.70±12.28	66.10±11.63	70.28±13.19	0.262	
Sex (female)	25 (49%)	15 (60%)	10 (40%)	0.691	
Sex (male)	26 (51%)	17 (65.4%)	9 (34.6%)		
Procalcitonin (ng/mL)	0.065 (0.05-0.14)	0.065 (0.05-0.151)	0.073 (0.05 - 0.146)	0.676	
hs-cTnT (ng/mL)	0.015 (0.009-0.027)	0.011 (0.005-0.015)	0.02 (0.016 - 0.039)	<0.001	
CRP (mg/dL)	17 (6.6-52)	16.2 (6.9-52)	18.45 (5.28 - 47.25)	0.955	
NT-ProBNP (pg/mL)	711 (149-4044)	200.5 (85-661.28)	4044 (1787 - 9384)	<0.001	
Secretoneurin (mmol/L)	141.96±38.97	132.33±41.57	158.17±28.31	0.011	25.84 (6.12 - 45.56)

hs-cTnT: high-sensitivity cardiac troponin-T; NT-ProBNP: N-terminal pro-brain natriuretic peptide; CRP: C-Reactive Protein

Table 2 . AUROC analysis of secretoneurin, N-terminal pro-brain natriuretic peptide and high sensitivity cardiac troponin T in the diagnosis of heart failure

	AUROC (95% CI)	p value
Secretoneurin	0.643 (0.457 - 0.828)	0.162
NT-proBNP	0.864 (0.739 - 0.99)	<0.001
hs-cTnT	0.759 (0.596 - 0.922)	0.011

hs-cTnT: high-sensitivity cardiac troponin-T; NT-ProBNP: N-terminal pro-brain natriuretic peptide

level was found to be significantly lower in the group without heart failure (mean: 132.33 ± 41.57) than in the heart failure group (mean: 158.17 ± 28.31), with a mean difference of 25.84 (95% CI: 6.12 - 45.56).

To evaluate the diagnostic utility of the biomarkers that exhibited statistically significant differences between the groups (NT-proBNP, hs-cTnT, and secretoneurin), receiver operating characteristic (ROC) analysis was performed (Table 2). The analysis revealed that the NT-proBNP level displayed excellent discriminative properties in distinguishing heart failure from no heart failure in patients presenting to the emergency department with dyspnea (AUROC: 0.864, 95% CI: 0.739 - 0.99, p<0.001). The discriminatory properties of hs-cTnT were found to be acceptable (AUROC: 0.759, 95% CI: 0.596 - 0.922, p=0.011). However, secretoneurin demonstrated no discriminative properties for this differentiation (AUROC: 0.643, 95% CI: 0.457 - 0.828, p=0.162).

Discussion

Our study aimed to investigate the potential of secretoneurin as a diagnostic biomarker for heart failure. The findings demonstrated that secretoneurin levels were significantly elevated in patients with heart failure compared to those without heart failure. This result suggests that secretoneurin is associated with heart failure, potentially revealing its prospective utility in diagnostic strategies.

This study adds to the emerging body of research that suggests secretoneurin's role in cardiovascular pathophysiology. It is known that the granin family of proteins, of which secretoneurin is a member, plays an important role in cardiac pathophysiology [13]. Based on the literature review, several studies have highlighted the role of secretoneurin in cardiovascular pathophysiology, particularly in heart failure. In a comprehensive review by Watanabe, 2021, it was noted that secretoneurin, a member of the chromogranin-secretogranin (granin) family of proteins, is elevated in patients with heart failure compared to healthy controls [14]. This observation aligns with our study findings, where we observed significantly higher secretoneurin levels in heart failure patients compared to those without heart failure.

Our findings build upon this knowledge, providing further evidence for the involvement of secretoneurin in heart failure. Yet, the intricacies of secretoneurin's role in the heart and its potential as a therapeutic tool warrant further investigation.

Moreover, Watanabe reported that high levels of secretoneurin are associated with an increased risk of mortality in patients with heart failure, aortic stenosis, or those undergoing various cardiac surgeries [14]. This suggests that secretoneurin may not only serve as a diagnostic biomarker but could also potentially be used as a prognostic marker in heart failure. However, our study did not investigate the prognostic utility of secretoneurin, and this could be an interesting avenue for future research.

Additionally, we examined the diagnostic potential of established heart failure biomarkers, hs-cTnT and NT-proBNP. Our findings were consistent with existing knowledge that these biomarkers are elevated in heart failure patients [15,16]. Our study further emphasized their diagnostic value by revealing their excellent and acceptable discriminative properties, respectively, in distinguishing heart failure patients from those without heart failure.

The ROC analysis performed in our study provided further insights into the diagnostic utility of these biomarkers. Despite a significant difference in secretoneurin levels between the two groups, secretoneurin did not display discernable discriminative properties. This indicates that although secretoneurin might be elevated in heart failure patients, it might not be sufficient on its own to distinguish heart failure from other conditions.

However, one noteworthy observation from this study is the comparable levels of secretoneurin in patients with heart failure, irrespective of gender and age demographics. This consistency across demographics indicates secretoneurin's potential utility as a supplemental biomarker in a comprehensive diagnostic approach, as it appears to be unaffected by demographic factors that can typically influence biomarker levels.

Moreover, it is essential to acknowledge the complex pathophysiology of heart failure, with multiple overlapping factors contributing to the disease state. Heart failure is often associated with other illnesses, such as sepsis and ischemic heart disease, which may also influence secretoneurin levels

[17,18]. This dual influence could potentially impact the discriminative properties of secretoneurin and may explain the results observed in this study. Further research is necessary to parse out these influences and provide more definitive insight into the role of secretoneurin in diagnosing heart failure.

Lastly, considering the findings of this study, it is intriguing to speculate about the future research directions in this domain. While secretoneurin may not have proven to be an effective standalone biomarker for diagnosing heart failure in this study, its elevated levels in heart failure patients could possibly indicate a more nuanced role in the pathophysiology of the disease. Further exploration of this role could lead to a more comprehensive understanding of heart failure and potentially pave the way for more advanced diagnostic strategies.

In conclusion, the present study provides valuable insights into the potential role of secretoneurin as a diagnostic biomarker in heart failure. Although it has not demonstrated robust diagnostic performance of NT-proBNP or hs-cTnT, secretoneurin still holds potential as an additional tool to be used in conjunction with existing biomarkers. Future research should delve deeper into understanding the intricate dynamics between secretoneurin, heart failure, and overlapping medical conditions to fully ascertain the clinical utility of secretoneurin in diagnosing heart failure.

Limitations

The study's limitations should be carefully considered. Although a statistically significant difference in secretoneurin levels between the groups was observed, the wide 95% confidence interval associated with the AUROC analysis introduces uncertainty regarding secretoneurin's discriminative abilities. This wide confidence interval can be attributed to the study's relatively small sample size, which limits the precision of the results. Additionally, the presence of a well-established biomarker, NT-proBNP, which has demonstrated good discriminatory performance for heart failure diagnosis, suggests that secretoneurin may not offer significant additional value as a stand-alone diagnostic tool. Further research with larger sample sizes is needed to provide more conclusive evidence regarding the discriminatory capabilities of secretoneurin compared to NT-proBNP.

Conclusion

In this study, secretoneurin demonstrated statistical significance as a diagnostic biomarker for heart failure, although it lacked the discriminative properties of established biomarkers like NT-proBNP and hs-cTnT. Therefore, while secretoneurin may not serve as a standalone biomarker, its potential utility as an additional tool in a comprehensive diagnostic approach necessitates further exploration.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

The authors declare no conflict of interest.

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How to cite this article:

Tahir Talat Yurttaş, Ali Cankut Tatliparmak, Sarper Yilmaz, Asım Bedri Erdem, Özgür Dikme, Özlem Dikme. Evaluating the Diagnostic Efficacy of Secretoneurin in Identifying Heart Failure Among Dyspneic Patients in the Emergency Department. *Ann Clin Anal Med 2023;14(11):1025-1028*

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